UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,592	05/03/2002	Audrey Goddard	P3230R1C001-168	4535

30313 7590 07/06/2005

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,592	GODDARD ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

Rejections of claim 6 are moot in view of the cancellation of the claim.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101/ 112, First Paragraph

Claims 1-5 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action.

Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above and in the previous Office action, one skilled in the art clearly would not know how to use the claimed invention.

Applicants arguments under 35 USC 101 support the request also to withdraw the related rejection under 35 USC 112, first paragraph, enablement (p. 25-26 of response). As a result, both utility and enablement arguments will be discussed here.

Applicants argue (p. 10) that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101. For reasons discussed at length in the previous Office action, even if the encoding polynucleotide has utility, on cannot on that basis alone support a utility for the encoded protein or antibody because the prior art provides sufficient support to make a correlation between mRNA and encoded protein level unpredictable *(e.g.*, Haynes et al.,

Electrophor. 1998, previously cited), especially in cancerous tissue (*e.g.*, see Hu et al., J. Proteome Res. 2003, previously cited).

Applicants argue (p. 10) that the Office cannot require experimental details to sufficiently establish utility of the claimed subject matter and the subject matter does not need to be "currently available". The argument has been fully considered, but is not persuasive. The Office is not requiring anything. The specification has failings which the Examiner pointed out. While current availability of a claimed invention is not always necessary, the invention must still meet the requirements of 35 USC 101 and 112, first paragraph. 35 USC 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...." For the reasons discussed here and in previous Office actions, it is maintained the specification does not contain an enabling disclosure or provide a specific and substantial credible utility or a well established utility, and the declarations included as exhibits in this case do not overcome the insufficiencies of the disclosure.

Applicants argue on pages 10-11 that *In re Brana* states that "Usefulness in patent law... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to administer to humans." The argument has been fully considered, but is not persuasive. *Brana* did deal with a rejection under 35 USC 112, first paragraph, however, the rejection was direct toward utility—specific, substantial and credible use. While it is true that administration of a pharmaceutical to a human is not always necessary for either utility or enablement, one must know how to use the invention without undue experimentation. In the instant situation, Applicants claim an antibody to the polypeptide of SEQ ID NO:82, of which it is maintained the disclosure does not enable the use because the further research and development needed involves undue experimentation and the specification has insufficient guidance or direction, for example, for enablement and utility as previously discussed.

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is a polypeptide

encoded by a nucleic acid with no known specific association other than that asserted by Applicants of higher expression in kidney and esophageal tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in kidney and esophageal tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical property. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though none as a tumor marker were identical or highly similar to SEQ ID NO:81. Therefore, the connection of SEQ ID NO:81 to tumors was not known. The prior art is silent with respect to activity of PRO1557 or its relationship to a family of proteins with conserved structure and function. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. The breadth of the claims is not at issue. There is very little guidance or direction about using the claimed antibody except that nucleic acid of SEQ ID NO:81 which encodes the cognate polypeptide is more highly expressed in kidney and esophageal tumors. As discussed in previous Office actions, the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

On pages 12-13, Applicants cite *Fujikawa v. Wattanasin* and *Cross* cases, arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo*. The argument has been fully considered, but is not persuasive. As stated in the previous Office action mailed 1/13/05, "At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled

artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: whether differences in nucleic acid expression of PRO1557 were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention."

Applicants argue (page 13) that there is a "significant probability" that the expression of the polypeptide will correlate with encoding nucleic acid expression and (p. 15, 20 and 24-27) that the Office did not present evidence to establish that there is not a reasonably expectation that the encoded polypeptide is more highly expressed in kidney and esophageal tumors than in normal matched tissue. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential art of record that requires the Examiner maintain that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:81 positively correlates with the expression of the protein of SEQ ID NO:82. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. As stated in the Office action mailed 1/13/04, "For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease." (p. 3) Indeed, there is evidence in the art to refute generalizations about gene/protein correlations. For example, Haynes et al. (Electrophoresis 19 : 1862-1 87 1 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1 863, second paragraph, and Figure 1). Haynes et al. provides evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al.

used yeast as an art-accepted model for eukaryotic systems. In a separate comparison by Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002) examining lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on p. 31300) it is stated, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." Fessler et al. warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." Given how small the unknown amount that DNA copy number of PRO1557 decreased in tumors, and the evidence provided by Haynes et al., Hu et al. and Fessler et al., one skilled in the art would not have assumed that a small decrease in gene copy number would correlate with significantly increased mRNA or polypeptide levels. The level of decrease of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO1557 polypeptide levels decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form

Applicants argue (p. 14, first section 3) that "it is likely that the PRO1557 polypeptides is differentially expressed in esophageal tumor and kidney tumor, and therefore antibodies to the PRO1557 polypeptide are useful as a diagnostic tool...." The argument has been fully considered, but is not persuasive. Were PRO1557 differentially expressed, were this expression significant and repeatable and were the information sufficiently complete to allow use of the polypeptide without undue experimentation, it would have utility as a diagnostic tool. It, however, has none of these necessities. There is no showing or reasonable expectation that PRO1557 is differentially expressed in certain cancers, even though its encoding nucleic acid of SEQ ID NO:81 appears to be more highly expressed in kidney and esophageal tumors, though specifically which kind and at what levels is unknown.

Applicants argue (pp. 15, 16 and 26) that the data in Example 18 as discussed in the Declaration of Grimaldi (submitted not here but in a similar case) demonstrates at least a two-fold difference in expression between normal and tumor tissues and the usefulness of the encoding nucleic acid as a diagnostic tool for determining the presence or absence of a tumor. The argument has been fully considered, but is not persuasive. The conclusory statement of Grimaldi of the necessary existence of an at least two-fold differentiation in nucleic acid expression does not support a utility for or enable the invention because it does not fill important gaps in the disclosure needed to use the invention without significant further experimentation, such as expression level range for normal and tumor tissues, specific types of kidney or esophageal tumors detectable, and probability of detection for any particular kidney or esophageal tumor type (*e.g.*, whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested), or if and how much the PRO1557 polypeptide is expressed in normal *versus* tumor kidney and esophageal tissue. Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues, this does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as "semi-quantitative" and the specification for Example 18 as "standard quantitative". The declaration also says (¶5) that "Data from a pooled sample are more likely to be accurate that data from a single individual." This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not

usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of kidney or esophageal tissue that can used, and other questions, the specification has not provided the invention in an enabling form. Therefore, even accepting Dr. Grimaldi's opinion (see first paragraph of p. 16 of response), the declaration is insufficient to overcome the rejections of the claims under 35 USC 101 or 112, first paragraph, for the reasons discussed above.

Applicants argue (pp. 17-18) that the results of Hu et al. (J. Proteome Res., 2003, previously cited) are not surprising and provide little if any information about genes with less than 5-fold differential expression tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are significant.

Applicants argue (p. 18) that Wu et al. (Gene, 2003, previous cited) shows that BNF-1, which shares an identical coding region with SEQ ID NO:81, is upregulated in breast, lung and colon tumors and its expression pattern is consistent with that of other oncogenes, supporting the use as a cancer diagnostic of the polynucleotide encoding the claimed antibody's antigen. The argument has been fully considered, but is not persuasive. First, Applicants are correct that vascularization of the tumor is not critical for usefulness as a marker of the tumor. However, while Wu et al. supports a use of the polynucleotide of SEQ ID NO:81 in breast, lung and colon tumors, Applicants assert overexpression in kidney and esophageal tumors. From the absence of listing of lung tumor in the table of EXAMPLE 18 for DNA64902-1667, it appears that lung tumor was analyzed for overexpression of SEQ ID NO:81 relative to normal lung tissue but no difference in expression was detected (see EXAMPLE 18 of the specification showing detection of other nucleic acids in lung tumor and the explanation that expression was analyzed using

cDNA libraries isolated from different tumor and normal human tissues). This discrepancy between Wu et al. and the instant application cannot be explained since, as Applicants point out (bottom of p. 23 of response), Wu et al. detected differences well below 5-fold. Also, the teachings of Wu et al., which were published after the filing of the instant application, cannot make up for the insufficiencies of the instant specification relating to lack of enablement of the instant invention for the reasons discussed in the previous Office action and above.

Applicants argue (pp. 20-22 and 26) that the declarations of Grimaldi and Polakis support the teachings in Molecular Biology of the Cell, Genes VI, and Zhingang et al. (2004), that it is generally accepted that mRNA and protein expression are positively correlated. The argument has been fully considered, but is not persuasive. As discussed above, there is sound data supporting evidence showing the unpredictability of saying level of expression of a particular nucleic acid will correlate with expression of the encoded protein. The argument of correlation between nucleic acid and protein expression has been previously addressed. Zhighan find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application, we have no correlation. There is no suggestion of multiple tumors tested. There are [0530] just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO1557 nucleic acid and/or protein. If Zhinghan et al. had obtained only a 5% correlation, it is doubtful the authors would have concluded that the nucleic acid would be a promising molecular marker.

Applicants argue (p. 22) that Meric et al. (Mol. Cancer Ther., 2002) says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this statement is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use as discussed above.

Applicants argue (p. 23) that according to the Grimaldi Declaration, even if there is no direct correlation between changes in gene expression and protein expression for PRO1557, an antibody to the polypeptide still has utility. Also, simultaneous testing between gene and gene product expression leads to better determination of suitable therapy. These conclusions are echoed in a declaration by Dr. Ashkenazi filed in a co-pending application, which supports the gene amplification data in the present application because even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, that in itself provides important information for cancer diagnosis and treatment. The argument has been fully considered, but is not persuasive. There is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification.

Applicants argue (p.23-24) that the teachings of Hanna et al. show that for Her-2, to diagnose breast cancer both gene product presence as well as amplification of the gene itself provides the most complete information. The argument has been fully considered, but is not persuasive. Hanna et al. say these testes are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, the issues of Her-2 cannot be generalized to any gene expressed in a tumor.

Applicants argue (*e.g.*, p. 25) that the claimed invention has a specific utility as a cancer diagnostic tool, in particular kidney and esophageal cancer. The argument has been fully considered, but is not persuasive. While it is agreed that the polynucleotide of SEQ ID NO:81 has this specific utility thought not enablement, it is not agreed that the polypeptide of SEQ ID NO:82 does. The reasons for this have been discussed at length above, but include relative or absolute levels of the difference(s) in PRO1557 protein level in tumor *vs.* normal kidney or esophageal tissue, the lack of information about particular tumor type (*e.g.*, adenocarcinoma

versus squamal), the lack of information about repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and the unpredictability of correlation mRNA and protein expression levels, it is maintained that the claimed invention is not supported by a substantial or specific utility nor is it enabled.

Applicants argue (*e.g.*, p. 26) that the role of a gene in a cancer is not necessary to enable its use as a diagnostic tool for tumor detection. The argument has been fully considered, but is not persuasive. It is correct that the role of a gene need not be known, but the specification and/or prior art needs to enable that particular gene to be used diagnostically. In this case, the prior art provides no information about the use of the gene for kidney or esophageal tumor diagnostics and the specification does not provide an enabling disclosure for use of the PRO1557 protein or antibody as a diagnostic tool for kidney or esophageal tumors based on differential expression for the reasons discussed above and in previous Office actions.

Claim Rejections - 35 USC § 102

Claims 1-5 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/70049 for the reasons set forth in the previous Office action.

Applicants argue that the instant application receives an effective filing date of 08/24/00 because the data of Example 18 was disclosed therein. The argument has been fully considered, but is not persuasive. Because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, as discussed above, and the earlier application likewise do not meet those requirements, the instant application does not receive benefit of priority to earlier filed applications. Even though SEQ ID NO:81 and 82 and the expression information of Table 18 were previously disclosed, enablement thereof has not been established as discussed above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 9:00AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
July 5, 2005

LORRAINE SPECTOR
PRIMARY EXAMINER